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Statement on imaging and pulmonary hypertension from the Pulmonary Vascular Research Institute (PVRI)

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Abstract (word count 153)

Pulmonary hypertension is highly heterogeneous and despite treatment advances it remains a life shortening condition. There have been significant advances in imaging technologies, but despite evidence of their potential clinical utility practice remains variable, dependent in part on imaging availability and expertise. This statement summarises current and emerging imaging modalities and their potential role in the diagnosis and assessment of suspected pulmonary hypertension. It also includes a review of commonly encountered clinical and radiological scenarios, and imaging and modeling-based biomarkers. An expert panel was formed including clinicians, radiologists, imaging scientists and computational modelers. Section editors generated a series of summary statements based on a review of the literature and professional experience and following consensus review, a diagnostic algorithm and fifty five statements were agreed. The diagnostic algorithm and summary statements, emphasise the key role and added value of imaging in the diagnosis and assessment of pulmonary hypertension and highlight areas requiring further research.

Introduction

Pulmonary Hypertension (PH) is highly heterogeneous, is challenging to diagnose and treat and has a survival worse than many forms of common cancer [1, 2]. It ranges from a rare form, pulmonary arterial hypertension (PAH) characterised by a vasculopathy and frequently severe elevation of pressure, to more common usually mild elevations of pulmonary artery pressure seen in severe cardiac and respiratory disease [3, 4]. The current system of classification identifies 5 groups, each with distinct pathophysiological characteristics [2, 3, 5]. The diagnosis of pulmonary hypertension is usually first suggested by echocardiography or chest radiography with confirmation of an elevated pulmonary artery pressure at right heart catheterization. Phenotyping is based on a careful history, blood testing for associated conditions, detailed physiological and imaging investigations.

The treatment of pulmonary hypertension is dependent on the underlying cause. For patients with PAH, drug therapy targeting imbalances in vasoconstrictor and vasodilator mediators, have been shown to improve exercise capacity, quality of life and event free survival [6-13]. However, PAH remains a life limiting and debilitating condition. In chronic thromboembolic pulmonary hypertension (CTEPH) pulmonary endarterectomy is an established technique with excellent long-term outcomes [14-18] and more recently drug therapy [19-21] and balloon pulmonary angioplasty [22, 23] have shown benefit in selected groups of patients with CTEPH. For patients with other forms of pulmonary hypertension, such as in association with cardiac and respiratory disease, trials of PAH therapies have thus far been disappointing [24-26]. Accurate classification is key not only as it defines treatment but also prognosis [27-29] and careful assessment is therefore crucial in the assessment of patients with suspected pulmonary hypertension.

Current assessment tools in the pulmonary hypertension clinic and end-points used in clinical trials may be limited by a number of factors. These include insensitivity to change, lack of repeatability and the invasive nature of tests. There is a need to identify new tools and end-points to aid the physician both in the clinical environment and in studies of new interventions [30-36]. Importantly over the last 20 years there has been major advances in imaging techniques and their application including the use of echocardiography, nuclear medicine, CT scanning, MRI and molecular imaging. There is growing evidence demonstrating the value of various imaging modalities in the classification, risk stratification, and follow-up of patients with pulmonary hypertension. Imaging studies have also provided insights into pathophysiological mechanisms [37-45].

The use of imaging varies across the globe due to a variety of factors including personal preference, availability and cost. Given the complex nature of certain imaging investigations there are also differences in methods of scan acquisition and post-processing within a given modality. Consequently, the PVRI have identified imaging as an important area for international collaboration, with the aim of developing evidence based statements and sharing best practice, whilst recognizing that approaches need to be tailored to imaging availability. This statement on imaging in pulmonary hypertension is aimed at physicians (including cardiologists and pulmonologists), pulmonary hypertension specialists, radiologists and imaging scientists.

Methods

The PVRI Imaging Task force met for the first time in Rome in 2016 with an aim to improve imaging practice globally in pulmonary hypertension. A summary statement from the PVRI was identified as an important first step in achieving this goal. Participants were invited from the existing PVRI membership in addition to international imaging experts. The group included representatives from wide ranging professional backgrounds and different geographical areas with varied access to imaging.

Groups of authors were assigned to specific sections to review current literature, identify summary statements and develop a diagnostic algorithm. An editorial board met to preview and refine summary statements and ensure uniformity of style (DGK, DL, JVC, AJS). To be included in the final document, summary statements required agreement of 80% of authors. Statements not meeting this requirement were reworded until this threshold was reached or the statement rejected. Given the rapid development of imaging technologies, the recommendations reflect a combination of published evidence, current practice, and expert opinion.

All authors read and approved the manuscript prior to submission.

Section 1: Imaging modalities used in the assessment of pulmonary hypertension

Chest radiography

Summary Statements

A chest radiograph is recommended as the initial imaging test in the assessment of unexplained breathlessness.

A normal chest radiograph does not exclude the diagnosis of pulmonary hypertension

Features of pulmonary hypertension include pulmonary artery enlargement and cardiomegaly.

Chest radiography

Patients with pulmonary hypertension frequently present with breathlessness. The principal role of the chest radiograph (CXR) is to identify other common causes of breathlessness (e.g. parenchymal lung disease, pneumonia, pulmonary oedema, pleural effusion, and pneumothorax). The findings of pulmonary hypertension on CXR vary. There may be enlargement of the central pulmonary arteries with pruning of the peripheral vessels, features that were observed in the majority of patients in a registry of patients with idiopathic pulmonary hypertension [46]. In addition, cardiomegaly and features suggestive of right atrial enlargement may be observed. However, a normal CXR cannot exclude the diagnosis, and the CXR may be normal, where pulmonary artery pressure elevation is modest. Radiographic features may also suggest the cause of pulmonary hypertension, such as upper lobe venous diversion and left atrial enlargement in patients with left heart disease, vascular plethora and peripheral pruning in patients with Eisenmenger physiology, and interstitial opacities in patients with diffuse parenchymal lung disease.

1.2: Echocardiography

Summary Statements

Echocardiography is the test of choice in the initial evaluation of suspected pulmonary hypertension

Echocardiography should include an assessment of pulmonary artery pressure, cardiac and valvular function

A probability of pulmonary hypertension should be generated using estimated pulmonary artery pressure and additional echocardiographic features

Doppler and 2D echocardiography remains the screening test of choice in the evaluation of suspected pulmonary hypertension [47-50]. Whilst right ventricular systolic pressure from the continuous wave Doppler of the peak tricuspid regurgitant velocity (TRV) is the most well-known tool for assessing the presence or absence of pulmonary hypertension, this metric can be subject to several limitations resulting in over or under estimation of the true pulmonary artery systolic pressure (PASP) [51]. Over the last decade, there have been many studies evaluating the role of clinically useful and readily available echo-Doppler parameters that allow one to move beyond the PASP and assess not just the likelihood of pulmonary hypertension, but also the hemodynamic underpinnings of the disease (ie. Left heart disease vs. PAH) [52, 53]. As noted in the most recent European Society of Cardiology (ESC)/European Respiratory Society (ERS) pulmonary hypertension guidelines, “echocardiography should always be performed when pulmonary hypertension is suspected and may be used to infer a diagnosis of pulmonary hypertension in patients in whom multiple different echocardiographic measurements are consistent with this diagnosis,” even in the absence of an elevated TRV [54]. This can then be used to generate a probability of pulmonary hypertension which will inform the diagnostic strategy and “decide the need for cardiac catheterization in individual patients” [54]. Furthermore, several echo-

Doppler parameters have been shown to have prognostic value in the setting of established pulmonary hypertension.

Clinically useful measures of pulmonary hypertension (ie elevated right ventricular afterload) on echocardiography include characteristics of the RV outflow tract (RVOT) pulse wave Doppler envelope such as a reduced acceleration time (< 100 ms) [53, 55-57], systolic notching [53, 58, 59], and pulmonary insufficiency velocity to estimate mean pulmonary artery pressures, as well as interventricular septal flattening (as characterized by the eccentricity index) [60], increased right to left ventricular ratio (0.8–1.0, 1.1–1.4, and ≥ 1.5 corresponding to mild, moderate and severe right ventricular dilatation, respectively) [52, 54], right ventricular hypertrophy and right atrial dilation [61] and measures of right ventricular function including tricuspid annular plane systolic excursion (TAPSE) [62, 63], and right ventricular fractional area change (RVFAC) [63-65]. While RVFAC is often limited in the setting of severe right ventricular enlargement [52, 63, 66], TAPSE is a reproducible measure of right ventricular function which measures the total displacement of the heart from the right ventricular base toward the apex in systole, and correlates with radionuclide-derived right ventricular ejection fraction [63]. TAPSE has also been shown to be prognostic of poor outcome in pulmonary hypertension in all-comers [62], as well as in follow-up assessment in a PAH population after initiation of pulmonary hypertension therapy [67, 68]. However, TAPSE has not been shown as an effective marker of right ventricular function in pediatric PH [69]. Other echocardiographic measures include the myocardial performance (Tei) index [70] and S' obtained from tissue Doppler imaging of the tricuspid annulus [71]. Markers of adverse outcomes include pericardial effusion and enlarged right atrium [72]. More recently, right ventricular longitudinal strain using 2D speckle tracking has been employed in the quantification of right ventricular function in patients with pulmonary hypertension, and has been shown to be impaired in patients with pulmonary hypertension, a predictor of mortality [73-76] and useful for assessment of therapy response [77, 78]. Lastly, given the complex anatomy of the right ventricle, recent investigation has focused on the use

350 of 3D echocardiography [79] and strain to assess global and regional right
351 ventricular structure and function and predict outcomes in pulmonary
352 hypertension [80].

Nuclear medicine imaging

Summary statements

A normal perfusion SPECT (single photon emission computed tomography) excludes chronic thromboembolic disease that will benefit from pulmonary endarterectomy and balloon pulmonary angioplasty. Ventilation and perfusion SPECT or SPECT CT is superior to planar scintigraphy.

In unexplained hypoxemia a nuclear medicine shunt assessment can be used to identify the presence of a right to left shunt.

In patients with suspected pulmonary artery sarcoma positron-emission tomography (PET) is recommended.

Ventilation/perfusion single photon emission tomography (V/Q SPECT) is recommended by the European Society of Cardiology (ESC) as the first line screening test for patients with chronic thromboembolic pulmonary hypertension (CTEPH) [1]. The technique is well established and has excellent diagnostic value particularly in the absence of lung disease. The perfusion image involves exposure to ionizing radiation and requires injection of 99mTc labelled macroaggregated human albumin (10-90microns in diameter) [20]. The macro-aggregated albumin becomes trapped within the small pulmonary arterioles, and a 3D image of pulmonary perfusion is acquired. In CTEPH typically peripheral wedge shaped defects of varying size are shown. Mismatch to ventilation can be confirmed by comparing ventilation and perfusion images. The added value of performing ventilation imaging is debated and in many centres perfusion imaging alone is performed and compared to CT which better demonstrates parenchymal lung disease. CTEPH may be missed on CT as attenuated distal vessels, subsegmental stenosis and webs may not be appreciated. Early studies demonstrated that scintigraphy was more sensitive than CT for the detection of CTEPH. However, given advances in technology, more recent studies have shown that CT pulmonary angiography and CT SPECT techniques are equally sensitive [21–23]. Dual energy CT or CT with iodine mapping allow construction of relative

perfusion maps in addition to providing angiographic images [81-87].
 Given that ^{99m}Tc labelled macroaggregates are trapped by small
 pulmonary arterioles, the presence of radioactive uptake in organs
 supplied by the systemic circulation (for example, the kidneys) can be
 used to identify the presence of a right to left shunt in hypoxemic patients
 with pulmonary hypertension [19].

Positron-emission tomography (PET) allows for observation of metabolic
 activity in the body which can be reconstructed to produce 3D images.
 Fluorodeoxyglucose (FDG), a glucose analogue, can be used to assess
 glucose uptake in tissues. PET scanning is commonly performed with
 simultaneous acquisition of CT and more recently with MRI for both
 functional and structural correlation [28]. In patients with suspected
 pulmonary artery sarcoma, PET will show high uptake allowing
 differentiation from chronic clot [29,30]. However, in acute clot FDG uptake
 may also be elevated, relative to unaffected vessels [88]. In PAH, uptake
 within the lungs and right ventricle have been demonstrated [24–27]
 although the clinical utility is uncertain.

Computed tomography (CT)

Summary Statements

CT provides a non-invasive evaluation of vascular, cardiac, lung
 parenchymal, and mediastinal structures in patients with known or
 suspected pulmonary hypertension
 Significant parenchymal abnormalities may be seen on CT evaluation in
 the presence of normal spirometry, particularly when there is a significant
 reduction in gas transfer factor
 CT pulmonary angiography to assess the pulmonary vasculature should
 be considered in patients presenting with pulmonary hypertension
 Imaging biomarkers from CT in patients suspected pulmonary
 hypertension should include measurement of pulmonary artery size, right
 to left ventricular ratio and left atrial size
 CT aids the classification of pulmonary hypertension

Computed tomography (CT) is increasingly recognized as a valuable imaging modality for the evaluation of known or suspected pulmonary hypertension. Advantages of CT include its widespread availability and accessibility, high spatial resolution, multi-planar imaging capabilities, and the ability to evaluate the pulmonary vasculature, lung parenchyma, cardiac, and mediastinal structures simultaneously.

CT evaluation of vessels

Pulmonary artery size can be easily measured and enlargement may suggest the diagnosis of pulmonary hypertension. Routine measurement is recommended particularly in patients at risk of pulmonary hypertension. For the diagnosis of pulmonary hypertension in lung disease a main pulmonary artery diameter greater than 29 mm had 84% sensitivity, 75% specificity, and 97% positive predictive value for pulmonary hypertension defined as a mean pulmonary artery pressure ≥ 25 mmHg [89]. The reliability of measuring the main pulmonary artery (PA) diameter and the ratio of the PA to aorta (Ao) ratio, has also been studied in suspected pulmonary hypertension. Investigators found that a PA:Ao ratio > 1 was 92% specific for a mPAP > 20 mmHg [90]. Other reports also support the use of pulmonary artery size in the clinical assessment of patients with pulmonary hypertension [91, 92]. However, it has been shown that an increase in pulmonary artery size also reflects disease duration and correlates only moderately with pulmonary arterial pressure [93]. It has previously been postulated that the presence of interstitial lung disease independently influences pulmonary arterial size [94], however, in a large cohort of patients with suspected pulmonary hypertension in association with interstitial lung disease, the presence and severity of interstitial lung disease did not influence pulmonary artery size which was found to be a useful diagnostic marker in patients with and without interstitial lung disease [95].

While contrast-enhanced CT angiography is the method of choice for the evaluation of suspected acute pulmonary embolism, its role in the

evaluation of the pulmonary vasculature in the setting of chronic thromboembolic pulmonary hypertension (CTEPH) has been a more recent development. Multiple findings are associated with CTEPH, including intravascular organising thrombi, webs, and regions of vascular narrowing or occlusion [96]. Mosaic perfusion of the lung parenchyma and enlarged bronchial arteries are also commonly seen [97-99].

Advanced CT capabilities have been studied in the evaluation of pulmonary hypertension. Dual-energy CT, provides an assessment of relative perfusion and improves the detection of peripheral vascular occlusion. In one study [85], dual energy CT showed 100% sensitivity on a per-patient basis compared to V/Q scintigraphy. However, there was imperfect agreement on a per-vessel basis. CT perfusion imaging may demonstrate residual perfusion abnormalities following therapy for acute pulmonary embolism, even in the absence of visualized thrombus on the angiographic portions of the study [100]. Perfusion imaging can also estimate cardiac output and in a small pilot study could detect pulmonary hypertension with high sensitivity and specificity [101, 102].

Pulmonary arterial hypertension is associated with vascular remodeling, including loss of arterial branching and increased vessel tortuosity. CT angiography can quantify these features, using fractal dimension and the ratio of actual vessel length to shortest linear distance to estimate tortuosity. Studies have shown these to correlate with hemodynamic measures in pulmonary arterial hypertension [103]. However, changes in the fractal dimension were found only in children with PAH, but not in adults [104]. Loss of distal vascular volume has also been described in patients with severe emphysema [105] and in patients with CTEPH [106].

CT evaluation of lung parenchyma

CT is the gold standard for the evaluation of the lung parenchyma. In a large registry series, CT measures have proven useful clinically in the assessment of patients with PAH [38]. Centrilobular ground glass opacities

are frequently seen in PAH and their presence on a CT performed for unexplained breathlessness should raise the possibility of this diagnosis [38, 107, 108]. Features of cardiac decompensation, pleural effusion/septal lines, and inferior vena caval size predict outcome [38]. The presence of emphysema or interstitial lung disease or bronchiectasis makes the diagnosis of pulmonary hypertension in association with lung disease likely. The addition of expiratory imaging is helpful to assess for small airways disease. CT may also identify features associated with rare conditions such as pulmonary veno-occlusive disease and pulmonary capillary haemangiomatosis (Section 2.2). This is an important differential diagnosis to idiopathic PAH because PAH therapy may be indicated but has a much higher risk of severe adverse effects than idiopathic PAH.

CT evaluation of cardiac structure and function

CT has historically not been used for the evaluation of cardiac structural abnormalities, as magnetic resonance imaging and echocardiography are the current modalities of choice. Nonetheless, many cardiac findings associated with pulmonary hypertension can be identified with non-gated contrast enhanced CT, including enlargement of cardiac chambers, thickening of the right ventricular free wall, and leftward deviation of the interventricular septum. CT can also identify structural abnormalities associated with congenital heart disease, such as partial anomalous pulmonary venous return and intracardiac shunts. Electrocardiogram-gated CT can be used to quantitatively assess right and left ventricular function. Additionally, a decrease in distensibility of the main pulmonary artery is highly correlated with the presence of pulmonary arterial hypertension [109-111]. A study has shown that dynamic contrast enhanced CT can measure the transit of contrast, correlated with cardiac output [102], and is associated with the presence of pulmonary hypertension [101].

CT evaluation of mediastinal structures

CT provides detailed imaging within the mediastinum and may demonstrate findings that give information as to the etiology or severity of

pulmonary hypertension. Dilatation of bronchial arteries is a common finding in CTEPH (73%), but less common in other forms of pulmonary hypertension (14% in idiopathic PAH) [97, 112]. A dilated esophagus in the setting of pulmonary hypertension suggests the diagnosis of systemic sclerosis. Other mediastinal findings, while not specific to a given etiology, may suggest a poor prognosis. These include the presence of pericardial effusion, lymphadenopathy, and reflux of contrast into the hepatic veins [38].

1.5: Magnetic resonance imaging (MRI)

Summary Statements:

MRI enables comprehensive cardiac evaluation in patients with suspected pulmonary hypertension

MRI is the gold standard technique for the assessment of biventricular morphology and function and is highly suitable for monitoring patients with pulmonary hypertension

MRI provides prognostic value in pulmonary arterial hypertension

MRI aids the classification of pulmonary hypertension particularly for left heart disease and chronic thromboembolic disease

Cardiac magnetic resonance imaging (MRI) is the gold standard for quantification of right ventricular volumes, mass, function, and flow hemodynamics in the pulmonary circulation [113, 114]. Cardiac MRI techniques allow for non-invasive assessment of right ventricular function and structure using high spatiotemporal resolution imaging sequences with high accuracy and reproducibility without exposure to radiation [113]. Furthermore, cardiac MRI can be used for assessment of myocardial tissue deformation properties (strain), global structural evaluation, and perfusion [115-117].

Right ventricular size and function

Right ventricular hypertrophy and dilation reflect an increased afterload⁵. Particularly, in advanced stages of pulmonary hypertension, a severely

dilated and functionally compromised right ventricle has a negative effect on left ventricular diastolic function by means of leftward septal shift and reduced left ventricular filling associated with decreased right ventricular stroke volume. Indeed, both right and left ventricular dimensional metrics have been shown to have diagnostic potential in treatment naïve patients with pulmonary hypertension and prognostic value in both adult and child populations [118-120]. MRI derived bi-ventricular functional and volumetric indices have been shown to have independent prognostic potential and differentiated incidental treatment naïve and prevalent patients in a large group of patients (n=576) [121]. Cine MRI derived indices including interventricular septal bowing, left ventricular eccentricity, and ventricular dyssynchrony due to prolonged right ventricular contraction time have been shown to correlate with invasive hemodynamics and are reflective of the overall hemodynamic condition and disease severity [122, 123]. Septal deviation measured by MRI is useful for the diagnosis of PH, but also in patients with left heart disease septal deviation >160 degrees can identify patients with elevated diastolic pulmonary gradient [124]. In addition MRI has proven useful in the diagnosis of pulmonary hypertension in patients with COPD, typically a challenging cohort for echocardiography [125].

Late gadolinium enhancement and T1 mapping

Late gadolinium enhancement (LGE) imaging is used to identify focal myocardial pathology but has also been applied to investigate regional myocardial disease in the right ventricle as a response to elevated mechanical stress. The predominant focus has been on the right ventricular free wall insertion sites to septum and how the extent of LGE corresponds to right ventricular morphological and dynamic changes [44, 45, 126-130]. Specifically, LGE was correlated with the reduced right ventricular function, dilation, mass, and regionally specific LGE was also inversely associated with reduced longitudinal strain [128, 131]. Additionally, the presence of delayed enhancement at the right ventricular insertion points has been associated with clinical worsening [127], though in a study using mortality as the end-point right ventricular insertion point LGE was not of independent prognostic significance. Extension of the LGE

into the interventricular septum was of prognostic significance at univariate analysis but was not significant at multivariate analysis [45]. A limited number of studies have explored the role of coronary arterial flow in pulmonary hypertension. [117, 132]. Features may be seen in patients with pulmonary hypertension with LGE imaging, however, its utility in the routine assessment of suspected pulmonary hypertension is not proven. LGE imaging can be considered where intrinsic cardiac disease is suspected.

T1 mapping is a quantitative method of assessing myocardial health. Native T1 mapping is performed without the use of contrast agents and has been shown to be an excellent differentiator between a healthy and diseased myocardium [133]. T1 has been shown to be elevated at the insertion points in pulmonary hypertension in animal [134] and human studies [135-137]. T1 correlates with markers of right ventricular remodeling [135] and septal position [138], however, no clear diagnostic or prognostic role has been identified in pulmonary hypertension [138].

Right ventricular Strain

Myocardial tissue deformation analysis has been assessed in patients with pulmonary hypertension [139-141]. Right ventricular morphology limits myocardial tagging and feature tracking to global longitudinal and circumferential deformation analysis. MRI based feature tracking has been shown to have prognostic potential and was associated with the severity of pulmonary hypertension [142]. Measuring left ventricular strain and torsion using tag MRI as part of ventricular interdependency and dyssynchrony investigations in CTEPH revealed left-right ventricular resynchronization post endarterectomy [143]. However, the clinical utility of deformation analysis is yet to be determined.

Pulmonary artery and aortic flow measurements

Phase-contrast MRI (PC-MRI) enables assessment of flow waveform in major vessels and allows for accurate $Q_p:Q_s$ assessment, necessary in patients with suspected congenital lesions [114]. Phase-contrast MRI of

pulmonary flow is recommended for assessment of right ventricular stroke volume due to variable tricuspid regurgitation and the challenges of contouring the right ventricle [144]. Relative area change of the pulmonary artery has been shown to be of clinical value [145, 146], and recently has been shown to be independent of right ventricular measurements and clinical data [37]. Black blood slow flow has been shown to be a strong diagnostic marker as the flow characteristics of the main and branch vessels are visualized [147, 148]. Four-dimensional flow MRI (4D-Flow MRI) is an emerging technique allowing evaluation of flow, vorticity and kinetic energy in any region of interest. Vortices have been noted in the main pulmonary artery of patients with pulmonary hypertension. The lifetime of the existence of a vortex has been shown to correlate with mean pulmonary artery pressure, and may have utility in the identification of pulmonary hypertension [149-152]. 4D flow also has the additional benefit that it allows retrospective flow evaluation by selecting a 2D slice in any plane of the 4D data set [153], whereas current techniques rely on the slice positioning at the time of the scan.

3D MR Perfusion and Angiography

MR-angiography can show characteristic vessel patterns in subtypes of pulmonary hypertension, including pruning in idiopathic PAH, thromboembolic obstruction and stenosis in CTEPH, and splayed vessels in chronic obstructive pulmonary disease (COPD)/emphysema [113]. MR-angiography is useful for the assessment of chronic embolus in the lobar and segmental pulmonary arterial vessels. Beyond the segmental level assessment of the pulmonary arteries with MR-angiography is very challenging [96]. In addition central embolus, particularly wall adherent clot can be missed if MR-angiography is reviewed in isolation, standard white blood MRI sequences can assist with visualization of central clot [96].

Dynamic contrast enhanced MRI perfusion is a promising technique for the assessment of chronic thromboembolic disease allowing visualization of pulmonary perfusion defects with sensitivity and specificity similar to that achieved with SPECT [39], with the advantages of higher spatial resolution

and lack of ionizing radiation. Time-resolved MRA or DCE can be used to measure passage of contrast bolus through heart and lungs to assess pulmonary perfusion [154, 155]. This can be used to measure mean transit time, time to peak, and blood volume [152, 156, 157].

1.6: Imaging in conjunction with invasive techniques

Summary Statements:

Catheter based angiography is used primarily to assess patients with chronic thromboembolic pulmonary hypertension considered as potential candidates for pulmonary endarterectomy or balloon pulmonary angioplasty

Performance of catheter based angiography requires skilled operators and should generally be performed in a pulmonary hypertension referral centre

Non-invasive imaging approaches can be used to select patients for pulmonary endarterectomy

Imaging measurements combined with catheter measurements may be used to study right ventricular pressure and volume relationships

Digital subtraction angiography

Catheter based angiography involves rapid imaging of the pulmonary arteries during the injection of contrast material through a catheter placed into the pulmonary arterial system [158, 159]. This used to be the primary method for evaluation of the pulmonary vasculature. However, given the development of CT and MR methods these modalities can also be used [96, 106, 160]. Catheter based angiography may be used at expert institutions for the evaluation of chronic thromboembolism prior to pulmonary endarterectomy and is required for balloon pulmonary angioplasty.

Assessment of ventricular-arterial coupling

Imaging can be incorporated with invasive catheter based methods for characterization of the mechanics of the right ventricle and the pulmonary

arteries. Flow and volumetric MRI measurements in conjunction with pressures obtained from right heart catheterization can be used for assessment of ventricular-arterial coupling [161-163]. One method for determining right ventricular contractility involves computation of the pressure-volume loop while using balloon occlusion of the inferior vena cava, permitting a preload independent assessment of ventricular contractility [164]. In practice this method requires use of conductance catheters or the measurement of pressure and flow at the same time in order to construct the pressure volume loops with different degrees of preload modulated by the occlusion of the inferior vena cava. Conductance catheters typically require calibration of the volume signal from imaging, typically a baseline cardiac MRI. The “Single Beat” method using a cardiac catheter can be used to estimate Pmax. This has been used in conjunction with MRI to measure ventricular volumes and can serve as a surrogate for Ees/Ea [165], the relative utility of information from these methods remains an area of research [166]. Cardiac MRI has been used to measure stroke volume and right ventricular volumes and in conjunction with pressure measurements to construct pressure-volume loops, and estimate right ventricular contractility [167-169] [170]. An entirely MRI-based non-invasive method of measuring right ventricular to pulmonary artery coupling has been proposed, defined by right ventricular stroke volume/right ventricular end-systolic volume, however, this holds similar information to RVEF (right ventricular stroke volume / right ventricular end-diastolic volume)[171]. Studies have suggested added prognostic value of coupling measurements [172, 173] although a recent large study suggested it did not add additional prognostic significance over right ventricular volume alone in patients with PAH [121].

Section 2: Imaging adults with pulmonary hypertension

2.1 The accuracy of cross sectional imaging to diagnose pulmonary hypertension and assess pulmonary haemodynamics

Summary Statements

A number of CT and MRI findings are characteristic of pulmonary hypertension

Current qualitative approaches to imaging cannot be used to confidently exclude the presence of pulmonary hypertension

Quantitative data obtained from imaging can be used to diagnose pulmonary hypertension and estimate pulmonary haemodynamics

CT imaging is widely available and measurement of the pulmonary artery size has been shown to correlate with mean pulmonary artery pressure [174], however, in established pulmonary hypertension there are progressive increases in pulmonary artery size over time [175]. Pulmonary artery enlargement may be seen in interstitial lung disease in the absence of pulmonary hypertension [94], although a recent publication has shown equivalent diagnostic accuracy in patients with and without interstitial lung disease. In patients with systemic sclerosis in the absence of interstitial lung disease a ratio of main pulmonary artery to aortic diameter of at least 1 was highly predictive of the presence of PAH although a normal ratio did not exclude PAH [176].

MRI is non-invasive, reproducible and is considered the gold standard for assessing right ventricular function [177]. Studies have shown a high correlation between right ventricular mass and ventricular mass index (VMI), the ratio of right to left ventricular mass, and mean pulmonary artery pressure measured at cardiac catheterisation [178, 179]. Recently investigators have shown that combining VMI and septal curvature improves the accuracy of estimating mean pulmonary artery pressure

[180]. By using MRI to calculate left atrial volume pulmonary arterial wedge pressure PAWP can be estimated allowing calculation of the trans-pulmonary gradient [180]. Cardiac output can be calculated from left ventricular volumetric measurements or phase contrast of flow in the pulmonary artery or aorta allowing an entirely non-invasive estimate of pulmonary vascular resistance based on individually derived MRI measurements. Models using right ventricular ejection fraction and average pulmonary artery velocity have also demonstrated accuracy for estimating catheter derived pulmonary vascular resistance [181]. Studies comparing CMR and right heart catheterisation in patients suspected of pulmonary hypertension have shown that an elevated VMI, reduced pulmonary artery velocity and the presence of increased gadolinium at the hinge points could predict the presence of pulmonary hypertension with a positive predictive value of >0.9 although no CMR measure could confidently exclude pulmonary hypertension [179]. In summary, although able to estimate pulmonary haemodynamics and identify pulmonary hypertension with high accuracy in certain groups, imaging is currently unable to exclude pulmonary hypertension.

2.2 How helpful is imaging in identifying the cause of pulmonary hypertension and subtyping?

Summary Statements

Different forms of pulmonary hypertension and their subtypes may exhibit characteristic imaging features

Echocardiography and MRI are useful for differentiation of pre and post capillary pulmonary hypertension

CT provides an accurate evaluation of lung structural abnormalities

Nuclear medicine, CT and MR perfusion imaging can be used to exclude chronic thromboembolic disease

Different combinations of imaging modalities can be employed tailored to local expertise and availability.

Many of the imaging findings associated with pulmonary hypertension are common to most or all disease processes leading to pulmonary hypertension. These findings may include enlargement of the central pulmonary arteries, right-sided cardiac enlargement, and abnormalities of lung attenuation. Some imaging findings, however, are more specific and can help to distinguish among the various causes of pulmonary hypertension. These are discussed in the following section.

Pulmonary Arterial Hypertension (group 1)

Within group 1 PAH, imaging findings may suggest a specific aetiology. Patients with systemic sclerosis typically have a dilated oesophagus, a central ground glass pattern and often associated interstitial lung disease. Drug and toxin exposures may also be associated with mild parenchymal fibrosis or mosaic lung attenuation. In patients with portopulmonary hypertension, the presence of varices, features of liver cirrhosis and splenomegaly are frequent. Anomalous pulmonary venous drainage should be sought as this is frequently associated with congenital heart disease in particular a sinus venosus atrial septal defect which is difficult to detect by transthoracic echocardiography. An interatrial shunt may also be suggested by contrast visualized entering the left atrium via the interatrial septum. While enlargement of the pulmonary arteries is common to all forms of PAH, it is greatest in patients with Eisenmenger physiology [38]. Patients with Eisenmenger physiology may also have laminated proximal thrombus and calcification within the wall of pulmonary artery. Bronchial artery enlargement is most frequently observed in CTEPH but is also observed in patients with congenital heart disease [182] and patients with IPAH and a BMPR-2 mutation [183]. Pulmonary veno-occlusive disease (PVOD) is rare and is characterized by mediastinal lymphadenopathy and interlobular septal thickening [184, 185], with or without associated findings of alveolar edema, mediastinal lymphadenopathy in the setting of a normal sized left atrium. Pulmonary capillary hemangiomatosis (PCH) is frequently associated with nodular foci of parenchymal infiltration. The triad of peripheral interlobular septal thickening, centrilobular ground-glass

opacities, and mediastinal lymphadenopathy has a good association with PVOD and PCH [184, 186, 187].

**Pulmonary hypertension due to left heart disease (group 2),
pulmonary hypertension due to lung diseases (group 3), and
pulmonary hypertension with unclear and/or multifactorial
mechanisms (group 5)**

Within these groups, imaging may be useful to identify either left-sided cardiac enlargement (group 2) or diffuse lung disease (groups 3 or 5). Many lung diseases will have a distinctive radiographic appearance allowing for specific diagnosis and grading of severity. Characteristic structural features of patients with left heart disease which can be visualized on both CT and MRI include left atrial enlargement [188-190], absence of posterior displacement of the interventricular septum [179] and relatively normal right ventricular volumes, although right ventricular enlargement is seen in more severe disease particularly in the setting of severe tricuspid regurgitation. The presence of valvular and coronary artery calcification and evidence of previous cardiac surgery are more common in left heart disease although may also be present in patients with other forms of PH. Echocardiography and MRI allow a comprehensive functional assessment. Patients with left heart disease have less right ventricular hypertrophy and compared to pre-capillary forms of pulmonary hypertension have better preserved right ventricular function. The absence of paradoxical septal motion / septal displacement in the setting of high right sided pressures infers an increase in left sided pressures. Echocardiography allows assessment of both systolic and diastolic dysfunction and the identification of valvular heart disease, in addition to identifying features suggestive of combined post- and pre-capillary disease [191].

**Chronic thromboembolic pulmonary hypertension (CTEPH) and other
pulmonary artery obstruction (group 4)**

A large prospective study estimated the risk of developing CTEPH after a pulmonary embolism at 3.8% at 2 years [192]. Imaging plays a critical role in the evaluation of suspected CTEPH, although the exact role of each imaging modality is debated. Some of this uncertainty reflects the rapid development of imaging technologies. Chest radiographs may suggest the diagnosis of CTEPH – with cardiomegaly, asymmetrical pulmonary artery enlargement, pruning of the vasculature and subpleural scarring – however, they are not diagnostic. Historically decisions on diagnosis and surgical management were based on V/Q scintigraphy and conventional pulmonary angiography with right heart catheterization. The role of V/Q scintigraphy (either planar or SPECT imaging) has changed. SPECT is recommended over planar imaging as it has higher diagnostic accuracy [193].

The current ESC/ERS guidelines recommend that V/Q scintigraphy be performed in all patients with suspected CTEPH [194]. These recommendations for V/Q scanning are in part based on clinical experience, previous recommendations and on older data [195-197]. This data demonstrated a significant improvement in the detection of CTEPH with scintigraphy compared to CTPA. However, rapid developments in CT technology have led to marked improvement in disease detection and characterization. More recent studies in experienced centres demonstrate that CTPA has high diagnostic accuracy for CTEPH [39]. Key imaging findings include identification of eccentric thrombus, intravascular webs, stenoses with or without post stenotic dilatation and occlusions. Bronchial artery dilatation (commonly described as a diameter of >2mm) is more commonly seen than in other forms of pulmonary hypertension. The presence of bronchial artery dilatation is associated with a better outcome following pulmonary endarterectomy. A mosaic perfusion pattern is seen in the vast majority of patients with CTEPH. Its presence should alert the observer to the possibility of CTEPH but should be differentiated from the mosaic pattern seen in small airways disease where often single or small clusters of lobules are involved in contrast to larger geographical areas typically seen in CTEPH. Performance of expiratory CT may be helpful in

887 this setting. Peripheral areas of sub-pleural scarring and cavitation
888 representing healed infarcts may also be seen in approximately 10% of
889 patients with CTEPH [198]. Dual-energy CT imaging generates maps of
890 regional iodine density in the lung parenchyma as a surrogate for
891 perfusion. This may further improve the evaluation of suspected CTEPH
892 by better demonstrating regions of decreased or absent blood flow [199],
893 and has been shown to have excellent agreement with SPECT [200].
894 Although the availability of this technology is relatively limited, iodine
895 mapping using CTPA with an unenhanced pre-scan is an emerging
896 technique, which generates a lung perfusion map. In contrast to dual
897 energy CT it does not require specialized hardware but involves
898 subtraction of unenhanced images from the contrast enhanced study. This
899 has the advantage that subtle abnormalities that may be missed on the
900 angiography are unlikely to be overlooked on a perfusion map thus
901 improving detection of subtle webs and distal disease [81].

902
903 By providing an assessment of the lung parenchyma and the mediastinum
904 CT can be helpful in identifying the presence of diffuse lung diseases and
905 emphysema (groups 3 and 5) and excluding pulmonary vascular
906 obstruction from a central mass. Parenchymal evaluation may also be
907 valuable in identifying features suggestive of interstitial oedema,
908 pulmonary veno-occlusive disease or vasculopathy though there is overlap
909 in the imaging features. CT may also identify features suggestive of large
910 vessel vasculitis or pulmonary artery sarcoma which may not be readily
911 appreciated on projectional angiography.

912
913 MR imaging can also provide an evaluation of the pulmonary vasculature
914 and is increasingly being used in select centers for the evaluation of
915 known or suspected CTEPH. 4D dynamic contrast-enhanced (DCE) lung
916 perfusion magnetic resonance imaging (MRI) techniques [201] are widely
917 available on current MRI systems and have shown excellent test
918 performance in diagnosing CTEPH in a single centre registry setting [39] .
919 In addition, a non-contrast, free breathing ventilation perfusion MRI
920 technique, known as the Fourier Decomposition (FD)-MRI method [202,

203] has recently shown initial encouraging results in diagnosing chronic pulmonary embolism [204], however, this technique needs to be confirmed in larger multicenter studies. Combined cardiac MRI and time-resolved MRA exam is suitable for detailed treatment response evaluation before and after pulmonary endarterectomy as well as balloon pulmonary angioplasty (BPA) in CTEPH patients [205, 206]

CTPA has largely replaced invasive catheter-based angiography as the initial morphological test for pulmonary arterial evaluation in most centers. However, catheter-based angiography may still have a role in the evaluation of CTEPH. Older data suggests that catheter-based angiography may provide a better assessment of the extent of pulmonary vascular obstruction than V/Q scintigraphy [207]. Additionally, some expert centers prefer catheter-based angiography for evaluation of the extent of thrombotic disease prior to PEA [208]. Again, CT performance relative to catheter-based angiography is generally poorer in older studies [159] compared to more recent data [209, 210]. This difference again likely reflects significant advances in CT technique and technology as well as greater awareness of CTEPH and its imaging features in imaging circles. When there is diagnostic uncertainty regarding the extent and distribution of chronic thromboembolic changes on the basis of a single imaging modality (usually CT) the use of a second morphologic imaging modality (MR angiography or catheter based angiography) may prove complementary by improving confidence in subtle lesions or identifying others. This can augment surgical decision making.

In recent years balloon pulmonary angioplasty has emerged as an effective therapeutic modality in selected patients with CTEPH. This has put greater emphasis on the evaluation of distal segmental and subsegmental vasculature. It is generally considered that at subsegmental level catheter based angiography out performs non-invasive morphological techniques (CT / MRI) which has resulted in increased utilization. Clinical criteria and imaging algorithms for the selection of patients for BPA vary between centres but catheter based diagnostic angiography for potentially

suitable candidates permits confirmation of suitable extent and distribution of disease as well as the patients ability to tolerate a BPA procedure (ability to maintain breathhold and tolerate the required period on the catheter table) [211].

2.3 Echocardiography and Cardiac MR - what are the advantages and disadvantages of each modality?

Summary statements

Echocardiography is more widely available, lower in cost and more portable than MRI

Echocardiography is superior to MRI for the evaluation of valvular heart disease and is more established in the assessment of diastolic function

Magnetic resonance imaging provides more accurate quantitative assessment of right ventricular morphology and function

Magnetic resonance imaging is more suited to serial assessment than echocardiography due to higher reproducibility

Echocardiography and CMR provide value in the assessment of patients with pulmonary hypertension. Echocardiography is well established in the initial assessment of patients with suspected pulmonary hypertension. It has also been evaluated in the serial assessment of patients with pulmonary hypertension [66, 67] and has been found to be prognostic and is recommended in current guidelines at follow-up and following treatment change.

Technical factors

Echocardiography has high temporal resolution, is widely available, low in cost, portable and less affected by arrhythmia than MRI although real time imaging [212] has helped to counter this limitation at the cost of lower spatial resolution. Echocardiography is more operator dependent and is less reproducible. MRI has the advantage that it has better contrast resolution and is able to image in any plane making it more suited to

accurately quantify right ventricular morphology and function. Furthermore, contrast imaging allows assessment of focal abnormalities of the myocardium and an assessment of myocardial perfusion [113, 116].

Estimation of pulmonary haemodynamics

In a systematic review of the literature the sensitivity and specificity for echocardiography for diagnosing pulmonary hypertension was 83% (95% CI, 73 to 90) and 72% (95% CI 53 to 85), respectively. However echocardiography is less accurate, in lung disease with sensitivity of 60% and specificity of 74% [213]. Empiric approaches have been used to estimate pulmonary haemodynamics using MRI [178, 180], In a recent study, mean pulmonary artery pressure was accurately estimated using multivariate regression analysis of MRI indices, with ventricular mass index and interventricular septal angle having additive value in model for estimation of mean pulmonary artery pressure [180]. It has recently been shown that with the inclusion of black blood pulmonary arterial slow flow in addition to ventricular mass index and interventricular septal angle high diagnostic accuracy can be improved further [147].

Right ventricular volumetric and functional assessment

Complete visualization of the right ventricle with echocardiography can be challenging, particularly in lung disease, preventing a complete volumetric evaluation of the right ventricle; this may be partially negated by the use of 3D echocardiography. MRI has the advantage of complete volumetric evaluation of the cardiac chambers with good reproducibility of volume, mass and ejection fraction [214] and is considered the gold standard for serial assessment of right ventricular volume and function [215]. Inaccuracies in segmentation of the right ventricle at the base of the heart and segmentation of ventricular trabeculations may be improved using threshold based approaches.

Echocardiography, using pulsed wave and tissue Doppler, is an established technique for the assessment of diastolic function. MRI phase contrast evaluation of the mitral annulus is feasible [216] and in a small

study imaging of the mitral valve annulus, in combination with mitral valve and pulmonary venous flow was as accurate as echocardiography [217]. Other techniques such as myocardial SPAMM tagging [218] and 4D three-directional velocity encoded MRI [219] have been used to evaluate left ventricular diastolic function. Long analysis times may reduce the applicability for routine clinical use.

Valvular heart disease

Pulmonary hypertension may occur in the setting of valvular heart disease. Echocardiography is the most useful non-invasive technique and has the advantage over MRI that it has high temporal resolution and allows accurate quantification of the severity of valvular heart disease. Left-sided valvular heart disease is a common cause of group 2 pulmonary hypertension. Contemporary studies suggest a prevalence of pulmonary hypertension of 30-40% in patients with mitral stenosis [220] upwards of 30% in patients with severe mitral regurgitation [221]; in asymptomatic patients, the presence of pulmonary hypertension serves as an indication for valve surgery [222]. With the emergence of transcatheter aortic valve replacement, pulmonary hypertension has been noted in up to 75% of patients with severe aortic stenosis[223]. Currently, echocardiography is the recommended non-invasive technique for the assessment of the presence and severity of valvular disease given its advantages over MRI including availability, low cost, high temporal resolution, widespread experience over many years. Despite this, there are instances in which echo is limited due to poor acoustic windows, lack of agreement across quantitative methods, significant inter- and intra-observer variability, which has led to interest in the emerging role of MRI in the assessment of valvular heart disease [224, 225].

2.4 Can imaging replace cardiac catheterisation in the assessment of suspected pulmonary hypertension?

Summary statements

Cardiac catheterisation is the gold standard for the measurement of pulmonary artery pressure

CT and MRI may suggest the diagnosis of pulmonary hypertension and quantitative MRI metrics can be used to confirm the presence of pulmonary hypertension with high accuracy

At diagnosis MRI and cardiac catheterisation provide equivalent levels of prognostic information

Cardiac catheterisation is currently the only way to identify patients with idiopathic pulmonary arterial hypertension likely to benefit from calcium antagonist therapy

Current ESC/ERS guidelines [226] recommend right heart cardiac catheterisation for the definitive diagnosis of pulmonary hypertension, assessment of intra-cardiac shunting and vasodilator testing in selected patients to identify the 10% of patients with idiopathic pulmonary arterial hypertension who may benefit from high dose calcium antagonist therapy. Measurements such as right atrial pressure, cardiac index and mixed venous oxygen saturation have prognostic value [227-229], and serial measurements are currently recommended to assess the response to therapy [226]. The procedure requires meticulous attention to detail but in expert hands is safe in adults with a morbidity of approximately 1% and mortality of 0.055% [230], although the risk of complications is significantly higher in children. Well established criteria at right heart catheter exist to assess patients with idiopathic pulmonary arterial hypertension likely to benefit from calcium antagonist therapy. However, no such criteria exist for imaging metrics.

Although current guidelines discuss the role of CT and MRI in the classification of pulmonary hypertension they are currently considered an adjunct and not yet considered a replacement for right heart catheterisation.

2.5 What is the role of imaging in assessing prognosis and response to treatment?

Summary statements

Echocardiography allows assessment of right ventricular function and measurements such as right atrial area, right ventricular fractional area change and tricuspid annular plane systolic excursion have prognostic value

CT imaging provides prognostic information in pulmonary arterial hypertension but its role in follow-up is currently limited by exposure to radiation

A number of CMR metrics have prognostic value and changes in CMR parameters at follow-up reflect changes in functional capacity and survival
Adjustment of right ventricular functional measurements for age and sex improves prognostication

Changes in right ventricular function measured by MRI have prognostic value

Echocardiography is widely available and a number of metrics have been shown to have prognostic value including right atrial area [231], right ventricular fractional area change, TAPSE [232-234] and the presence of a pericardial effusion [231, 235]. Echocardiography is widely used, in many centres to assess the response to treatment, acknowledging issues of operator dependency and reproducibility.

Several measurements made at CTPA including right ventricular to left ventricular ratio, right atrial size and a posteriorly deviated inter-ventricular septum predict prognosis in PAH subgroups whilst the presence of pleural effusions, septal lines and increased inferior vena cava area were independent predictors of a worse outcome in PAH at presentation regardless of subgroup [38]. Although this may be helpful at presentation to guide urgent assessment and introduction of emergency therapies the availability of other imaging modalities and associated radiation exposure necessitates that CT is not recommended in the assessment of treatment response.

In contrast, the highly reproducible nature and non-invasive and non-ionising nature of MRI makes it an ideal modality to assess treatment response and in the EURO-MR study [236] changes in MRI measured cardiac index and right ventricular ejection fraction correlated with changes in WHO functional class and survival. A study examining changes in CMR parameters demonstrated that this was a better predictor of outcome than pulmonary vascular resistance measured invasively at cardiac catheterisation [215]. MRI metrics including increased right ventricular volumes, reduced left ventricular volumes, stroke volume, cardiac output and pulsatility of the vasculature predict a worse outcome in PAH although there is currently no large study comparing the prognostic value of CMR and right heart catheter measures.

2.6 How can we improve imaging techniques to make them more acceptable to patients?

Summary statements

Minimising radiation dose by the use of non-ionising techniques where possible and implementation of dose reduction protocols will reduce the risks to patients
Involvement of patients in investigative decision making will allow a more tailored approach to investigation

Whilst plain chest radiographs and echocardiography are generally well-tolerated and acceptable examinations, cross sectional techniques do have some specific limitations and issues, in particular radiation doses for CT and claustrophobia for MRI.

The diagnostic information provided by CT needs to be balanced with the radiation dose. In a life shortening illness concerns regarding radiation exposure rarely impact on the decision to perform CT imaging at the time of diagnosis. Advances in dynamic imaging, with improved temporal resolution, has provided hope that gated CT can challenge MRI in the assessment of cardiac function, however, such examinations typically

involve higher doses of radiation. Using iterative reconstruction, dose reduction can be achieved [237]. In fact, large reductions in dose to less than a third the dose of standard acquisitions have been achieved without loss of image quality using iterative reconstruction [238], and the use of dynamic Z axis collimation has been shown to further reduce dose [239].

Limitations of MRI include long scanning times, scanner noise and frequently patients feel claustrophobic (5%) leading to incomplete examinations. Developments to reduce scanning time, eg. novel rapid imaging techniques and limiting the study to the most clinically relevant sequences may help. The more widespread installation of wide bore scanners may help to reduce claustrophobia and make MRI a more acceptable imaging modality for all patients. The use of media entertainment may improve acceptability to patients. More patient involvement in discussions around the implications of the tests are needed. Patient participation is advised to determine the issues most relevant to patients to help develop imaging services.

Section 3 Imaging pathway for suspected pulmonary hypertension in adults

3.1 Current guidelines

The ESC/ERS guideline on diagnostics and therapy of pulmonary hypertension review current imaging modalities and make a number of recommendations for incorporation in a diagnostic strategy [2]. Echocardiography is recommended as a first-line non-invasive diagnostic investigation in case of suspicion of pulmonary hypertension. Chest x-ray and high-resolution CT are recommended in patients with high or intermediate probability of pulmonary hypertension following echocardiography and high-resolution CT should be considered in all patients with pulmonary hypertension. Ventilation/perfusion or perfusion lung scan is recommended in patients with unexplained pulmonary hypertension to exclude CTEPH. Contrast CT angiography of the pulmonary arterial circulation is recommended and pulmonary (catheter based) angiography should be considered in the workup of patients with CTEPH. There are no recommendations for the use of MR imaging as part of the diagnostic strategy or algorithm and no discussion of emerging techniques [240] [241] . Current American College of Chest Physicians guidelines on pulmonary hypertension provide no specific recommendations on employing imaging as part of a diagnostic strategy in patients with suspected pulmonary hypertension [242]. The Cologne Consensus Conference 2016 provides no additional imaging guidelines.

3.2 PVRI diagnostic imaging pathway (Figure 1)

Initial assessment and identification of risk factors

In patients presenting with symptoms and or signs suggestive of pulmonary hypertension a detailed history and the results of basic tests are key in determining the diagnostic strategy. Risk factors for treatable

forms of pulmonary hypertension (PAH and CTEPH) must be sought as their presence reduces the threshold for further imaging. Basic investigations including an electrocardiogram, lung function with gas transfer factor and a plain radiography may suggest an alternative diagnosis [194] or increase the probability of pulmonary hypertension. Further investigation may not be required when a confident alternative diagnosis can be made.

Echocardiography

Echocardiography is the recommended first line imaging modality in the assessment of suspected pulmonary hypertension and allows evaluation of cardiac structure and function and an estimate of pulmonary artery pressure. Following echocardiography, patients should be stratified into those at low, high or intermediate probability of pulmonary hypertension according to ESC/ERS guidelines [194].

Sub-optimal echocardiography

For patients with a sub-optimal echocardiogram, imaging with CMRI can be used to identify patients at increased risk of pulmonary hypertension although currently used metrics cannot confidently exclude mild pulmonary hypertension [147]. A number of metrics on CTPA have been shown to reflect elevated pulmonary artery pressures in addition to providing information on other potential causes for breathlessness, and although evidence is limited this may be considered in selected patients [91, 95].

Low probability of pulmonary hypertension from echocardiography

For symptomatic patients identified as low probability from echocardiography, further assessment is dependent on the presence or absence of risk factors. For those with risk factors for CTEPH, perfusion lung imaging is recommended using CT imaging (CT-LSIM or DECTA), nuclear medicine techniques (ideally SPECT), or MRI perfusion imaging [39, 81, 86, 243]. If risk factors for PAH exist, the diagnostic strategy will be dependent on the risk factor; in systemic sclerosis, given the high prevalence of PAH in symptomatic patients, further evaluation is advised

and a number of screening regimens exist such as DETECT [244]. For other at risk patients an interval echocardiographic examination may be appropriate [194].

High or intermediate probability of pulmonary hypertension from echocardiography and assessment for left heart disease

For patients at intermediate or high probability of pulmonary hypertension, the echocardiogram should be evaluated for evidence of left heart disease such as significant valvular heart disease, left ventricular systolic or diastolic dysfunction. If present the history should be re-reviewed to assess for risk factors for left heart disease (hypertension, obesity, coronary artery disease, diabetes mellitus, atrial fibrillation). Where risk factors for PAH or CTEPH are absent and risk factors for left heart disease present, pulmonary artery pressure modestly elevated, left atrial size increased, no paradoxical septal motion and / or significant right ventricular dysfunction present, then no further investigation to assess for pulmonary hypertension may be required. However, where risk factors for PAH or CTEPH are present, right ventricular function is severely impaired, systolic pulmonary artery pressure is severely elevated (≥ 70 mmHg) and / or paradoxical septal motion exists, then further investigation to exclude other causes of pulmonary hypertension should be considered [26]. If no features of left heart disease exist patients should undergo CT pulmonary angiography if no contraindications exist.

CT pulmonary angiography

Where left heart disease is excluded or if present and other causes of pulmonary hypertension cannot be confidently excluded, then cross sectional imaging with CT including CT pulmonary angiography should be considered as it can aid in (i) assessment of the likelihood of pulmonary hypertension, (ii) classification of disease (identifying features of co-existing lung disease or left heart disease) and (iii) identification of patients with CTEPH [38]. If features of CTEPH are identified at this stage, patients should be referred directly to a centre experienced in the management of pulmonary hypertension for further evaluation.

1276

1277 **Perfusion lung imaging**

1278 If CTPA is sub-optimal, indeterminate, or is performed by a centre not
 1279 experienced in the assessment of pulmonary hypertension and CTEPH is
 1280 not identified, in the absence of significant parenchymal lung disease,
 1281 perfusion lung imaging (Q-SPECT or 3D MR perfusion) is advised at this
 1282 stage. CT lung subtraction iodine mapping (CT-LISM) or dual energy CT
 1283 (DECT) in addition to directly visualising abnormalities in the pulmonary
 1284 arterial tree also allows construction of perfusion lung maps, preventing
 1285 the need for other forms of perfusion lung imaging to exclude CTEPH [81,
 1286 86, 199, 245].

1287

1288 Where patients have rapidly progressive symptoms and a high probability
 1289 of pulmonary hypertension from echocardiography, physicians should not
 1290 delay referral to expert centres until the above investigations are
 1291 completed. Supplementary investigations including tests to assess for
 1292 conditions associated with PAH such as connective tissue disease and
 1293 HIV infection should be considered [1, 194].

1294

1295 **Review and integration of imaging investigations with other tests and**
 1296 **assessment for respiratory disease**

1297 Following imaging, the results should be integrated with the patient's
 1298 clinical characteristics. CT imaging may identify unexpected findings such
 1299 as thromboembolic disease or parenchymal lung disease. Given the
 1300 current lack of evidence for specific interventions targeting the pulmonary
 1301 vasculature for patients with pulmonary hypertension in the context of
 1302 respiratory disease current therapies should be aimed at the underlying
 1303 condition, recognizing that the presence of pulmonary hypertension
 1304 identifies patients at increased risk of death; where appropriate options
 1305 such as transplantation should be explored. In patients with respiratory
 1306 disease with risk factors for PAH or CTEPH, significant right ventricular
 1307 dysfunction or severe elevation in systolic pulmonary artery pressure
 1308 (≥ 70 mmHg), referral to a PH centre should be considered; selected
 1309 patients may be entered into studies or receive a trial of therapy. In

addition to pulmonary vascular phenotypes increasingly recognized in respiratory disease [4, 246, 247], these patients may have other forms of pulmonary hypertension such as undiagnosed connective tissue disease or CTEPH [247]. Where uncertainty exists, discussion or referral to a pulmonary hypertension centre is recommended.

Referral or discussion with a pulmonary hypertension referral centre

Pulmonary hypertension referral centres provide an environment where specialists are experienced in the assessment of patients with suspected pulmonary hypertension. They also provide specific therapies and support for people affected by pulmonary hypertension. Imaging investigations will be reviewed and where sub-optimal may be repeated. At this stage further investigation will usually be dependent on the pre-test probability of different forms of pulmonary hypertension. See Table 1. For patients considered for treatment, cardiac catheterization is recommended.

CTEPH suspected

For those with evidence of CTEPH on CTPA or with risk factors such as previous pulmonary embolus, deep venous thrombosis, splenectomy, or pacemakers, further evaluation of (i) the pulmonary vasculature with DSA or MRA, (ii) lung perfusion, with SPECT or 3DMR perfusion, DECTA/CT-LISM, (iii) lung ventilation, (iv) biventricular function, with CMR or 3D echo and (v) coronary or further cardiac valvular assessment, if risk factors for ischaemic heart disease exist or co-existent valvular heart disease is noted, and the patient is considered a candidate for pulmonary endarterectomy, may be performed. The choice of investigations are also dependent on the preference of pulmonary hypertension referral centre, where pulmonary endarterectomy or balloon pulmonary angioplasty, is being considered. Right heart cardiac catheterisation with measurement of pulmonary arterial wedge pressure and pulmonary vascular resistance will aid decisions regarding appropriateness of the intervention and to confirm the presence of pulmonary hypertension. Where filling defects extend into the proximal pulmonary artery and or right ventricular outflow tract other

conditions such as sarcoma should be considered and FDG-PET-CT may be helpful [248, 249].

Patients with risk factors for specific forms of pulmonary hypertension

In patients with risk factors for specific forms of PAH, further investigation should be tailored; ultrasound examination of the liver with portal Doppler ultrasound should be performed in patients suspected of underlying liver disease / portal hypertension. In cases where congenital heart disease is suspected (features such as anomalous pulmonary venous drainage or atrial septal defect may have been detected on CT or transthoracic echocardiography), transoesophageal echocardiography and or CMRI to estimate Qp:Qs ratio and cardiac catheterisation with a saturation run should be considered [250, 251]. In patients with PH where the cause is felt to primarily related to left heart disease or respiratory disease right heart catheterization may be required to assess disease severity particularly if a trial of treatment is contemplated. Further assessment of right ventricular function in these patients may be helpful, particularly where the echocardiographic assessment of right ventricular function was challenging; findings at cardiac MRI of preserved or mildly impaired RV function or a normal septal angle in PH-LHD (suggesting the absence of a pre-capillary component) may negate the need for right heart catheterization [124].

Unexplained pulmonary hypertension

Where no obvious cause of pulmonary hypertension exists, following review of imaging and integration with other clinical characteristics, cardiac catheterisation with vasodilator testing should be performed to identify the 10% of patients with idiopathic PAH who have a fall in mean pulmonary artery pressure or at least 10 mmHg to <40 mmHG with no reduction in cardiac output, who may respond to treatment with high dose calcium channel blockers [194].

Unexplained hypoxaemia

Hypoxaemia in pulmonary hypertension is uncommon at the time of diagnosis in the absence of respiratory disease, a right to left shunt or a severely reduced gas transfer factor. If a right to left shunt is suspected a bubble echocardiogram, renal perfusion SPECT or MRI (time resolved imaging or Qp:Qs) should be considered.

Monitoring of patients at follow-up

Following diagnosis follow-up assessments of right ventricular function are recommended to aid risk stratification [119, 215] in combination with a clinical assessment and a measurement of exercise capacity. Cardiac MRI or echocardiography can be used to assess right ventricular function. In selected cases follow-up cardiac catheterization may be performed.

Section 4.0: Imaging children with suspected pulmonary hypertension

Summary statements

Echocardiography is recommended as the initial imaging investigation in children with suspected pulmonary hypertension

Performance of cardiac catheterization in children frequently requires general anaesthesia and is associated with a higher risk of complications than in the adult population

Diagnostic imaging strategies differ in children compared to adults reflecting significant differences in disease aetiology

MRI is of additional value in the initial evaluation and follow-up of pulmonary hypertension in conjunction with other non-invasive techniques such as echocardiography.

Imaging techniques should be modified where possible to provide adequate diagnostic information whilst avoiding anaesthesia.

4.1 Introduction

Imaging provides valuable information that aids the management of patients with pulmonary hypertension, from diagnosis and accurate phenotyping, through to monitoring disease and assessing response to therapy. The majority of imaging modalities in medicine and their implementation in hospital environments have been developed with the needs of adult patients in mind. Whilst the underlying philosophy and principles of imaging in children are the same as in adult pulmonary hypertension there are some challenges which may be more pertinent to imaging children. With appropriate modification these can be overcome.

4.2 Differences in the spectrum of disease between adults and children:

Whilst pulmonary vascular disease pathophysiology is very similar, the context in which it occurs in children is often very different to adult cohorts of pulmonary hypertension. Most notably children are much more likely to have pulmonary hypertension in the context of congenital or

developmental abnormalities whereas in adult populations comorbid diseases of aging may be more important. Large cohorts of paediatric patients with pulmonary hypertension demonstrate that pulmonary hypertension related to congenital heart disease and pulmonary hypertension related to developmental lung disorders predominate with idiopathic pulmonary arterial hypertension responsible for approximately 20% of published cohorts and chronic thromboembolic pulmonary hypertension responsible for less than 1% of cases.[252] Furthermore approximately 30% of children with pulmonary hypertension have more than one potentially causal association.[253] Finally, in a large proportion of children with pulmonary hypertension the pulmonary hypertension is associated with other rare conditions. Taken together this means that the pre-test probabilities of different pulmonary hypertension aetiologies differs from that in adults. This in turn affects the overall diagnostic imaging strategy. A diagnostic algorithm for children has recently been published following the World symposium of pulmonary hypertension, and reflects differences between adults and children.[254]

4.3 Scale

The paediatric period covers a period from birth to adulthood. The body undergoes enormous growth and development during this period of time and body size can increase by almost two orders of magnitude. Organ structure, function, maturity and complexity continue to develop through childhood and again enormously during puberty, profoundly affecting physiology.

The most obvious change through childhood is in size. This produces challenges when aiming to distinguish normal organ size from abnormal, for example ventricular volume. A number of approaches have been adopted to address this challenge. The first is to establish normative data for children throughout childhood and express these in terms of centile charts or standard deviation (Z) scores. Normative values in echocardiography in large populations of healthy children are increasing with normative echocardiographic values published in pediatrics with

Boston z-scores.[255, 256] Normative values in cardiac MRI in large populations of healthy children is challenging and normative data are sometimes lacking. A second approach is to adopt ratio-metric relationships, that is, the parameter in question is simply divided by a measure of body size e.g. BSA or is expressed as a ratio against another cardiovascular parameter in the same patient, e.g. pulmonary artery to aorta size ratio; yet these approaches have significant limitations. A more appropriate and physiologically sound approach to scaling may be to adopt allometric scaling relationships. This approach divides the cardiovascular variable of interest by the body size variable raised to a scalar exponent in the form x/y^b . There are data across a huge range of scales and species which show empirically that this approach eliminates the effect of body size on cardiovascular structure and function. This approach to scaling or normalisation has not been widely adopted and therefore the relevant scaling exponents are not well established or accepted.

The effect of scale on imaging resolution

By definition, in children spatial scales of structures are smaller (i.e. children are smaller) and temporal scales are typically shorter (i.e. children have higher respiratory rates and higher heart rates). This therefore affects imaging quality at any given spatio-temporal resolution. While some adaptations are possible for example higher frequency ultrasound probes for echocardiography other imaging modalities suffer from fundamental physical and engineering limits to their spatial temporal resolution. Table 2 suggests some approaches which may improve spatio temporal resolution of imaging modality such that they are suitable for smaller patients.

4.4 Intellectual/emotional maturity

Many imaging modalities require the cooperation of the patient to achieve optimal imaging results. Children are often emotionally and intellectually less mature than adults, thus securing their cooperation can be more challenging and time-consuming. One approach to this which is widely

used is to sedate or anaesthetise children, however, sedation and anaesthesia in children with pulmonary hypertension is associated with a substantial risk of morbidity and mortality and it is desirable to avoid this wherever possible. Imaging in an appropriate environment with adequate time and support, e.g. play therapist involvement, time to familiarize patients with the environment can substantially improve cooperation and imaging quality. Distraction techniques and allowing parents into the imaging room are extremely helpful.

4.5 Echocardiography in Pediatric Pulmonary Hypertension

Echocardiography is used as the initial screening diagnostic imaging for the diagnosis of paediatric pulmonary hypertension and the most important non-invasive tool that is used for routine assessment. [47, 48, 252, 257-259] It is used for continued follow-up and medication management.[260] Developments in echocardiography in the past two decades have led to new insights into the structure and function of the right ventricle and its role in various diseases including pulmonary hypertension.[261, 262] Conventional imaging includes assessment of anatomy in two-dimensions (2D), hemodynamics via Doppler echocardiography, and qualitative and quantitative evaluation of right ventricular (RV) and left ventricular (LV) function.[47, 48, 258, 260, 263-265] Advanced echocardiography includes evaluation of right heart size and function, myocardial mechanics, and estimated RV to pulmonary arterial (PA) coupling ratio.[266-270] Table 3 shows the advantages and limitations of each of echocardiographic techniques used in paediatric pulmonary hypertension. In recent years, different echocardiography parameters have been found in small studies to be useful in identifying high-risk patients who are likely to develop adverse clinical outcomes [269, 271-274]. Table 4 demonstrates the echocardiographic views needed to obtain the functional parameters in paediatric pulmonary hypertension.

4.6 Cardiac Magnetic Resonance Imaging in Pediatric Pulmonary Hypertension

Cardiac MRI remains the gold standard imaging modality for assessment of bi-ventricular function and volumes in pediatric pulmonary hypertension.[252] MRI derived functional and volumetric indices predict morbidity and mortality in pediatric pulmonary hypertension and may provide additional information with respect to inter-ventricular interactions [120, 275]. In addition, phase-contrast MRI remains the state-of-the-art flow imaging technique enabling precise flow volume quantification and consequently provides valuable assessment of Q_p/Q_s ratios in children with pulmonary hypertension associated with congenital heart disease and intracardiac shunts. Furthermore, parallel or sequential phase-contrast MRI and pressure evaluation in the catheterisation lab has been proposed as a novel and potentially more reliable method for the calculation of pulmonary vascular resistance in comparison to standard Fick principle or thermodilution [276, 277]. Recent studies suggest that pulsatile pulmonary vascular stiffness indices derived by phase-contrast MRI and ultrasound may have a strong prognostic potential to predict both hard and soft outcomes in pediatric pulmonary hypertension [278-280]. Lastly, MRI angiography can aid with differential diagnosis by fine characterization of the pulmonary vasculature and exclusion of thrombi. Unlike echocardiography, cardiac MRI is currently not suitable for frequent serial assessment due to its clinical availability, longer post-processing time, and also due to necessary anesthesia required for younger children and neonates.

In summary, children pose a different set of challenges to adult populations when it comes to imaging. Given the proven benefits of imaging adults with pulmonary hypertension it is appropriate that all patients including children are allowed to experience these benefits. Appropriate adaptations to imaging strategy and environment can achieve high quality results in the vast majority of paediatric patients.

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Section 5 Future Directions

5.1 Applications of computational modelling and AI in pulmonary hypertension

Summary statements

Physiological modelling can be used to characterise the behavior of the cardiopulmonary system.

Computational models assessing pulmonary artery flow have high diagnostic accuracy in suspected pulmonary hypertension

Machine learning approaches may assist image segmentation and improve diagnostic and prognostic assessments.

Further work to assess computational approaches versus current diagnostic approaches in pulmonary hypertension is recommended.

Imaging modalities and markers derived based on images alone have been shown to have clinical potential. Their interpretation could be enriched by introducing additional knowledge from the application of mathematical models, which can bring insights into the haemodynamic system behaviour in health and disease.

Based on mathematical and physical principles, models of the pulmonary circulation are currently being evaluated in the translational/clinical research. Electrical analogue (Windkessel or 0D-zero-dimensional) models supplied by patient-specific 2D phase-contrast MRI data have been proposed [281, 282] to globally characterise the pulmonary circulation in terms of vascular resistance and compliance in healthy and PH patients. They have also shown promising results for quantifying the changes of the electric parameters in patients with PAH, at baseline and follow-up [283]. Wave transmission (one dimensional 1D) models are

particularly powerful, as “waves carry information”, and the energy [282, 284, 285] contained in the backward reflected wave can be used as an indicator between the right ventricle and its afterload mismatch. Using a 1D model of a straight elastic tube and temporal MRI flow and area waveforms, it has been shown that on average, more than 40% of the total wave power was contained in the backward wave measured in patients with PH, whereas less than 20% was characteristic to the healthy volunteers group [282]. Different PH heterogeneities can be mimicked by modifying the structural and elastic parameters of a 1D pulmonary tree structure. Several authors [285-287], investigated the pressure and flow waveforms in healthy and several simulated PH conditions, using numerical solutions of 1D models of the major vessel network. Notably, Qureshi et.al [285] changed the configuration of the structured tree and altering, in turn, the compliance of the large and small vessels to predict the haemodynamic changes induced by PAH, CTEPH and HLD. The authors showed an increase in the reflected waves under these simulated conditions, with the potential to differentiate between different PH phenotypes.

The 0D and 1D models have the main advantage that are relatively simple to implement and do not require significant computing resources. However, three-dimensional, 3D computational fluid dynamics (CFD) models are more complex, being able to provide patient-specific characterisation of haemodynamics [288, 289]. Full 3D CFD simulations can resolve the physiological flow field in all three directions and time. Further post-processing of the CFD results can provide computed metrics (for example wall shear stress (WSS)), which give additional insights on disease progression. It has been argued [290] that pathological flows in the pulmonary artery alter cell behaviour favouring vasoconstriction. 3D CFD [291, 292] studies of the pulmonary circulation showed that shear stress has an impact on endothelial health and dysfunction, and reduced WSS in the proximal pulmonary arteries were shown to be characteristic to PH patients.

Machine learning of RV contours to derive tissue motion has shown to be of prognostic value in PAH and of greater significance than standard cardiac volumetric metrics [293]. Such approaches are of great potential, minimizing user input / error and potentially providing a more complete prognostic assessment. The added value versus measurements adjusted for age, sex and body surface area [118, 294], or standard CMR strain parameters in PAH is an area for further work. Machine learning approaches may significantly improve the automation and quantification of parameters from imaging. For example, deep learning approaches have already been utilized for automation of arterial-venous segmentation of the pulmonary circulation [295].

The success of the computational models is closely related to the available data from the imaging modalities. Regardless of using the data only to supply the models' boundary conditions, or integrate it within artificial intelligence algorithms [296, 297], the computational models and imaging modalities play together an essential role in the process of non-invasive PH diagnostic, prognostic and understanding of the disease mechanisms.

Section 6 Conclusion and areas of research priority

In this statement we have discussed recent advances in imaging techniques in pulmonary hypertension and their clinical application. This is summarised in the PVRI Imaging Task Force diagnostic algorithm. Rapidly evolving technologies also provide opportunities to improve our understanding of pulmonary hypertension and assess the impact of much needed new therapies. This section identifies areas requiring further research in addition to highlighting a number of on-going and planned studies.

6.1 Establishment of normative ranges and repeatability of imaging techniques

Despite the widespread use of imaging techniques in clinical practice there is only limited data on the impact of age, sex and ethnicity on commonly used metrics. The studies conducted to develop normative equations to allow for correction have been performed [298-304]. However, given the significant impact of age, sex and ethnicity on morphological characteristics, more research in this area is warranted to understand variation across populations.

There is increasing interest in using imaging end-points in clinical trials to assess treatment response in the clinic setting. However, there is limited data on the repeatability of cardiac MRI measurements. The RESPIRE study (clinicaltrials.gov), which should report in the 3rd quarter of 2019 will provide information on the sensitivity to change relative to measurement repeatability of cardiac MRI morphological and functional data. This will aid the design of studies considering MRI as a primary end-point. Even in the absence of such data, studies such as REPAIR (clinicaltrials.gov) are now using imaging to assess the impact of pharmacological interventions. The results of these studies are awaited with interest.

6.2 Comparison of imaging modalities and approaches

There are pros and cons of different imaging modalities with respect to diagnostic performance, repeatability, availability, exposure to ionising radiation, acceptance to patients, and cost. Often new imaging modalities and or approaches are introduced into clinical practice with limited data. The cost of conducting large comparative studies and the rapid advances in the underlying technology, that may occur during the conduct of a study, may impact negatively on decisions to conduct such comparative studies. However, there is a pressing need to perform such technology appraisals. An important area is the diagnosis of CTEPH, where there have been significant advances in the imaging of the pulmonary vasculature. Additional data is required to critically evaluate these new techniques and challenge current guideline approaches. Importantly a number of studies are planned, including the prospective, multicentre, comparative phase III diagnostic trial CHANGE-MRI, a European multi-centre study comparing functional MRI and VQ-SPECT. This study aims to recruit 1000 patients (clinicaltrials.org). The INSPIRE study is a pilot non-inferiority study comparing iodine subtraction mapping with VQ-SPECT in patients with suspected CTEPH (clinicaltrials.gov). A prospective study comparing the cost and utility of follow-up approaches using echocardiography and cardiac MRI in patients with PAH is highly desirable.

An additional important area of research is the optimisation of initial diagnostic testing and follow-up based on imaging availability, particularly where imaging and invasive testing are limited

6.3 Combining imaging with other modalities (Genetics and MRI augmented right heart catheterisation)

With advances in genetics and imaging there is an opportunity to better understand genotype phenotype associations that have the potential to aid clinical decision making. Heterozygous mutations in the gene encoding bone morphogenic protein receptor type 2 (BMP2) are the most common genetic cause of pulmonary arterial hypertension, occurring in ~15% of cases [185] and have been associated with worse right

ventricular function on cardiac MRI [305]. Bi-allelic mutations in the eukaryotic translation initiation factor 2 alpha 5 kinase 4 gene (EIF2AK4) are described in pulmonary veno-occlusive disease and pulmonary capillary haemangiomatosis [306, 307], which are important to diagnose given their worse prognosis and poorer response to PAH therapies. In a large international cohort study [185], patients with PVOD were diagnosed based on radiological criteria, however, a number of patients who were carriers of EIF2AK4 were not identified by imaging alone. These patients were younger and had a lower gas transfer factor and greater interlobular septal thickening and mediastinal lymphadenopathy. This suggests that combining imaging with genetic testing in at risk patients has the potential to improve diagnostics and prognostication. Integration of genetics, clinical data and imaging is an exciting area for further research.

Diagnosis and accurate prognostication in patients with pulmonary vascular disease remains challenging. Haemodynamic data from right heart catheterisation provides important information with direct pressure measurement. However, it does not provide a complete morphological or functional assessment of the right ventricle and pulmonary circulation. MRI augmented catheterization involves invasive right heart catheterization performed inside the MRI system [276, 308, 309]. It combines simultaneous invasive hemodynamic and MRI morphological and functional assessment in a single radiation-free procedure, providing detailed physiological insights. Further work to investigate the potential advantages in terms of clinical utility, improved understanding of disease, patient acceptability and cost is recommended.

6.4 Improving our understanding of pulmonary vascular disease by assessing the distal vasculature and using novel imaging approaches

A limitation of current imaging modalities in pulmonary hypertension is the insensitivity to visualise and interrogate the distal pulmonary arterial vasculature, the primary site of disease in patients with PAH. Assessing pulmonary perfusion directly using novel MR or CT methods may provide

a significant insight to the underlying small vessel vasculopathy. Temporal and spatial heterogeneity of the blood flow in patients at baseline and during PAH therapy is an area for further research.

Inhaled Xe¹²⁹ hyperpolarised gas imaging is an emerging technique. Reports of hyperpolarised gases in CTEPH have suggested a potential role in follow-up of patients [310] and abnormalities in idiopathic PAH have also been reported [311]. A patient inhales Xe¹²⁹ gas and ventilation images are acquired. Xe¹²⁹ possesses relatively high solubility in tissues and blood. The transit of the gas from gas to dissolved phase can be probed using MRI spectroscopy. This allows the acquisition of functional parameters characterizing the gas exchange as well as gas uptake by imaging the dissolved-phase. By studying these Xe¹²⁹ diffusion properties, various microstructure parameters including alveolar-volume ratio, blood-gas barrier thickness, and surface-to-volume ratio can be determined.

6.5 Stress imaging of the cardiopulmonary system

Imaging in patients with suspected pulmonary hypertension is usually undertaken at rest but there is increasing interest in evaluating changes in pulmonary artery pressure and right ventricular function on exercise and following other acute interventions. Exercise echocardiography is well described [312-315] in the assessment of patients with pulmonary hypertension, but currently its use is not widespread. There is increasing interest in using cardiac MRI and augmented MRI right heart catheterisation to assess cardiopulmonary system on exercise to determine the differential response of RV morphology and function in health and disease. Further evaluation of the effect of acute interventions such as fluid and acute vasodilator challenges would also be of value.

6.6 Artificial intelligence (AI) and applications in pulmonary hypertension

With the rapid development in machine learning technologies, there is huge potential to improve imaging assessments. Image acquisition, analysis and interpretation are areas that may benefit from integration of

AI technologies. There are a number of recent publications in this area [293, 296, 297]. Notable areas for further research include acceleration of MRI acquisition, improved segmentation of the cardiac chambers on CT and MRI and the pulmonary vasculature on CT and diagnostic and prognostic classification and interpretation.

6.7 The impact of imaging on patients and users

Much of the focus of imaging research is based on the knowledge that can be obtained by the images themselves. However, an important area of investigation is the impact of imaging; on patients and their families, physicians and healthcare professionals, researchers who interpret the images and health care systems that fund imaging. The acceptability, emotional impact and cost of clinical pathways to diagnose and serially assess patients requires further research, including the relative tolerability, risks and benefits of different imaging approaches. A study evaluated the social and technological epistemology of clinical decision making as mediated by imaging [316]. This study illustrated that images can fulfil a mediating role by aiding acquisition of knowledge and facilitating communication in addition to illustrating the highly social aspects of interactions with patients and within multidisciplinary meetings. Involvement of patients and their families and users of imaging is required if imaging is going to fulfil its potential.

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1814 **Conflict of interest**

1815 The authors declare that there is no conflict of interest.

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Tables

Table 1 Recommended imaging investigations in adults with pulmonary hypertension considered for specific pulmonary vascular interventions

	Imaging investigations
All patients	Echocardiography CTPA or DECTA or CT-LSIM Perfusion lung imaging in selected patients (see section 3.2)
Liver disease suspected or known	Ultrasound scan of liver with portal Doppler
Congenital heart disease suspected or known	Consider: CMRI with Qp:Qs Transoesophageal echocardiogram
Left heart disease or respiratory disease	CMRI or further echocardiographic studies to assess right ventricular function may reduce the need to proceed to cardiac catheterisation
Suspected CTEPH	Consider: MR angiography or digital subtraction angiography Lung ventilation If malignant obstruction suspected FDG-PET CT recommended
Unexplained hypoxaemia	Consider: Bubble Echocardiography Renal Q SPECT CMRI Qp:Qs MR time resolved imaging
Follow-up of right ventricular function	Echocardiography CMRI

CTPA=CT pulmonary angiography, DECTA=Dual energy computed tomography angiography, CT-LSIM=computed tomography lung subtraction iodine mapping, CMRI, cardiac magnetic resonance imaging, Qp:Qs= Pulmonary-Systemic Flow Ratio, FDG-PET CT = fluorodeoxyglucose-positron emission tomography computed tomography, SPECT= Single Photon Emission Computed Tomography

Table 2 Imaging modalities used in paediatric pulmonary hypertension

Modality	Adaptation	Problem
Echocardiography	Higher frequency probes provide better spatial and temporal resolution in children. Optimised sector width and focal length improves image quality in children.	High heart rate, small structures but better echo windows reduced distance from probe to structure of interest
CT imaging	Multislice	Small structures, high heart rates, movement, difficulty in breath holding, need to avoid sedation anaesthesia
MR imaging	Rectangular field of view, partial Fourier encoding, patient friendly MR environment, use of novel real-time sequences/undersampling with novel reconstruction	Small structures, high heart rates and respiratory rates, movement and difficulty breath holding, need to avoid anaesthesia

CT=computed tomography, MR=magnetic resonance

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Table 3: Echocardiographic variables used at diagnosis and follow-up in paediatric pulmonary hypertension

Echo Variables	Interpretation	Advantage	Limitations	References
Interventricular septal flattening	Mild, moderate, or severe to indicate the severity of pulmonary hypertension	Quick visual assessments when there is not adequate TR peak velocity to estimate RVSP	Qualitative. Can occur in systole and diastole depending on pressure or volume overload Poor validation with clinically relevant measures	[317, 318]
TR peak velocity (m/s)	$RVSP = SPAP = 4(TR\ max)^2 + \text{mean RA pressure (mRAP)}$. If TR velocity is $>3\text{m/s}$, PH may be suspected	Easy to obtain	75% is measurable modest correlation with systolic pulmonary artery pressure	[319]
Mean PAP (mmHg)	$mPAP = 4V(\text{early peak pulmonary})$	Alignment of PR maybe	PR required for measurement	[260, 263]

	regurgitation velocity) ² + RAP	better than TR	modest correlation with mean pulmonary artery pressure not substitute for cardiac catheterisation	
Diastolic PAP (mmHg)	DPAP = 4 V(end-diastolic pulmonary regurgitation velocity) ² + RAP	Alignment of PR maybe better than TR	PR required for measurement	[260, 263]
TAPSE (mm)	Longitudinal systolic function	Easy to obtain, impaired RV systolic function when the TAPSE is < than 2 standard deviation of age related value	Single dimension, does not take into account of the circumferential or radial function of the RV. Alignment can be a problem Poor correlation with RV function and survival	[320, 321]
PAAT (ms)	Abnormal PAAT values with z-score < -2	Can easily be measured in all patients	HR dependent	[256, 322]

	SD were predictive of PH.			
RV TDI E' (cm/s)	< 8cm/s may indicate increased risk of mortality	Can easily be measured in all patients	HR dependent	[323]
RV TDI MPI	Abnormal TDI MPI values indicates right ventricular dysfunction	Can easily be measured in patients	HR dependent	[324]
S/D ratio	>1.4 indicates severity of PH and increased risk of mortality	Can easily be measured from TR velocity	Presence of defined TR velocity in systole and diastole	[272]
End-systolic RV/LV ratio	>1 may indicate increased risk of adverse events in pediatric pulmonary hypertension	Easy to obtain clinically	Cannot be used in patients with left to right shunts.	[325]
RV FAC (%)	Decreased FAC (<35%) correlates with decreased	Clinically easy to obtain	Does not take into account of the entire right ventricle	[324]

	systolic function			
3D RV EF (%)	Decreased RV EF (<45%) indicates decreased RV function	Full volume datasets to evaluate for right ventricular volumes and function. Accurate measurements of right ventricular function and can be prognostic in pulmonary hypertension	Required breath holding for adequate volumes. Can be difficult even in single beat acquisitions when the pediatric probe is too big.	[268, 326]
RV strain (%)	RV free wall longitudinal strain decrease indicates decreased systolic RV function.	RV free wall longitudinal strain maybe more sensitive in detecting ventricular function and is prognostic in pulmonary hypertension	May not have adequate frame rate when the heart rate is too high.	[273]
LV EF (%)	LV EF may be decreased in severe	Quantification of LV function	Bi-plane Simpson's may not be accurate as	[324]

	pulmonary hypertension via RV-LV interaction		the LV is distorted in severe PH,	
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TR=tricuspid regurgitant, RVSP=right ventricle systolic pressure, SPAP=systolic pulmonary arterial pressure, V=velocity, RA=right atrium, PH=pulmonary hypertension, RAP=right atrial pressure, DPAP=diastolic pulmonary arterial pressure, PAAT=pulmonary arterial acceleration time, SD=standard deviation, TDI=tissue Doppler imaging, MPI=Myocardial performance index, FAC=fractional area change, RV EF=right ventricle ejection fraction, LV EF=left ventricular ejection fraction

Table 4: Echocardiographic views to obtain functional parameters in paediatric pulmonary hypertension

	View	Functional Parameters
Anatomy	Parasternal short axis	End-systolic RV/LV ratio [325]
Doppler	Parasternal short axis	Pulmonary acceleration time/ejection time Pulmonary regurgitation early and late diastolic velocity
	Apical chamber 4-	Tricuspid regurgitation severity (none, mild, moderate, severe) Tricuspid regurgitation peak velocity Myocardial performance index (tricuspid tissue Doppler) [327] Systolic/diastolic (S/D) duration ratio from TR Doppler[272] Tissue Doppler systolic and diastolic velocities (tricuspid, septal, mitral)
Right atrium	Apical chamber 4-	Right atrial area (RA)
Right ventricle	Apical chamber 4-	Qualitative RV function (good, mildly/moderately/severely depressed) RV end diastolic and end-systolic dimensions indexed for BSA (2D) Fractional area of change (FAC) % Tricuspid Annular Planar Systolic Excursion (TAPSE) with z-score (M-mode when available, 2D) RV strain (global and segmental) [43, 326, 328] 3D RV volumes and function [268, 326]
Left ventricle	Apical chamber 2+4	LV ejection fraction (bi-plane Simpson or 5/6 area-length method) LV eccentricity index[317] LV strain (global) [329] 3D LV volumes and function [324]
Other		Presence and severity of pericardial effusion (none, small, moderate, large)[231]

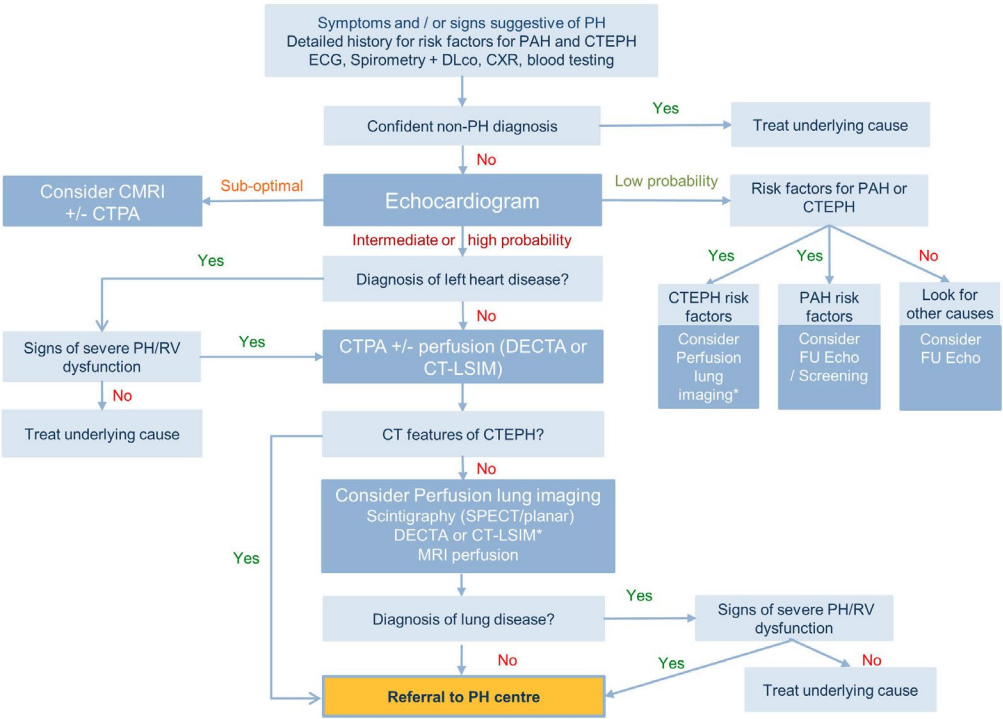
RV=right ventricle, LV=left ventricle, TR=tricuspid regurgitant jet BSA=body surface area,

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Figures

Figure 1 PVRI diagnostic algorithm

Figure Legend: Please see section 3.2 pages 38-44 for detailed description of how to navigate the algorithm.



Abbreviations: PH: pulmonary hypertension, PAH: pulmonary arterial hypertension, CTEPH: chronic thromboembolic pulmonary hypertension, ECG: electrocardiogram, DLco: diffusing capacity of the lungs for carbon monoxide, CXR: chest radiograph, CMRI: cardiac magnetic resonance imaging, CTPA computed tomography pulmonary angiography, DECTA: dual energy computed tomography pulmonary angiography, CT-LSIM: computed tomography lung iodine subtraction mapping, SPECT: single photon emission computed tomography, RV right ventricular. In this algorithm patients are classified into low, intermediate and high risk of pulmonary hypertension according to ESC/ERS guidelines [2].

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